SYSTEMATIC REVIEW

Antithrombotic treatment for peripheral arterial disease

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Context: Patients with peripheral arterial disease (PAD) bear a substantial risk for vascular events in the coronary, cerebral and peripheral circulations. In addition, this disorder is associated with a systemic milieu characterised by ongoing platelet activation and heightened thrombogenesis.
Objective: To determine the optimal antithrombotic prophylaxis for patients with PAD.
Data sources: Using terms related to PAD and antithrombotic agents, we searched the following databases for relevant articles: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the National Institutes of Health Clinical Trials Database, Web of Science, and the International Pharmaceutical Abstracts Database (search dates: 1 January 1990 to 1 January 2007). Additional articles were identified from cardiovascular and vascular surgery conference proceedings, bibliographies of review articles, and personal files.
Study selection: We focused on randomised trials, systematic reviews and consensus guidelines of antithrombotic therapies for PAD.
Data extraction: Detailed study information was abstracted by each author working independently.
Results: Multiple studies show that patients with PAD manifest platelet hyperaggregability, increased levels of soluble platelet activation markers, enhanced thrombin generation and altered fibrinolytic potential. Many of these markers predict subsequent cardiovascular events. Available randomised trials and meta-analyses show that most available antithrombotic agents prevent major cardiovascular events and death in patients with PAD, including aspirin, aspirin/dipyridamole, clopidogrel, ticlopidine, picotamide and oral anticoagulants.
Conclusions: Although the most favourable risk-benefit profile, cost-effectiveness and overall evidence base supports aspirin in this setting, we provide scenarios in which alternatives to aspirin should be considered.

Recent estimates suggest that nearly 30 million people are affected by peripheral arterial disease (PAD) in North America and Western Europe.[1] In older patients, or those with risk factors such as diabetes mellitus or smoking, the prevalence of PAD approaches 20–30%.[2] This disorder is important in several aspects. The local occlusive process underlying PAD worsens progressively in a substantial number of patients (about 25% in the first 5 years after diagnosis), and such individuals often require vascular intervention despite optimal medical treatment.[1] A smaller subset progress to major amputation (about 1%/year). Interventions comprise the largest portion of economic costs in this condition.[3]

Of equal importance, PAD is often associated with atherosclerosis in other vascular areas and patients with the disorder are at markedly increased risk for vascular events and death.[4] PAD also confers a negative effect on health status and quality of life, similar in degree to disabling angina or heart failure.[5] Finally, because of shared antecedents, PAD commonly clusters with other major comorbidities, including chronic obstructive lung disease, heart failure, diabetes mellitus, dementia and atrial fibrillation.[6–8]

PAD AND THROMBOGENESIS

As with other manifestations of atherosclerosis, platelets and clotting factors play a pivotal part in the progression of PAD and the genesis of complications. Many studies have suggested that patients with PAD manifest platelet hyperaggregability, increased levels of soluble platelet activation markers, enhanced thrombin generation and altered fibrinolytic potential (summarised in table 1).[9–23] These findings, which are consistent across the different stages of PAD, have important ramifications. Individually, many of the markers characterising the prothrombotic environment of PAD are predictive of future cardiovascular events.[24–26] Komarov *et al*, for instance, showed that patients with PAD with a D-dimer concentration in the fifth quintile had a 14-fold greater risk of cardiovascular events than those with a D-dimer in the first quintile, even after adjusting for confounders.[25] Moreover, such rises correlate strongly with the severity of PAD and predict deterioration of symptoms and physical function. Taken together with the increased cardiovascular risk posed by PAD, these data underline the importance of considering antithrombotic prophylaxis in all such patients.

SELECTION OF ANTITHROMBOTIC TREATMENT

A variety of antithrombotic agents have been studied in patients with PAD. These include antiplatelet drugs (such as aspirin, thienopyridines and picotamide) and oral anticoagulants, specifically, coumarins (table 2). New evidence is available for many of these approaches, and recent guidelines have added considerable clarity.[27–29] On the basis of randomised trials and systematic reviews, the various therapeutic options are discussed in detail below, starting with the most widely prescribed agent, aspirin.

TREATMENT OPTIONS

Aspirin

Acetylsalicylic acid (aspirin) has a large and distinguished evidence base for preventing myocardial infarction and stroke in patients with cardiovascular disease, perhaps best summarised in the Antithrombotic Trialists' Collaboration (ATC) third systematic overview.[41] This report included 42 randomised trials of antiplatelet treatment in 9214 patients with PAD,

Abbreviations: ATC, Antithrombotic Trialists' Collaboration; OAC, oral anticoagulants; PAD, peripheral arterial disease

Table 1 Studies on markers of platelet function and coagulation in patients with peripheral arterial disease

Study	Sample	Key findings: PAD *v* controls
Cassar[9]	60 PAD/40 controls	Higher P-selectin expression and platelet fibrinogen binding
Catalano[10]	30 PAD/40 controls	Higher TM levels
Cortellaro[11]	50 PAD/58 CAD or CVD controls without PAD	Higher D-dimer and lower tPA antigen and fibrinolytic capacity; D-dimer and fibrinolytic capacity predictive of subsequent vascular events
Devine[12]	29 PAD/10 controls	Higher anti-factor XIII α-chain binding to platelets
Gosk-Bierska[13]	59 PAD/26 controls	Higher vWF, fibrinogen, TAT and PF4
Gresele[14]	63 PAD/18 controls	Higher urinary 11-dehydro-thromboxane B2 levels
Handa[15]	18 PAD/19 controls	Higher TM, fibrinogen, α1-AT and TAT; lower α2-PI levels
Killewich[16]	69 PAD/11 controls	Higher PAI-1 and tPA antigen; lower tPA activity
Koksch[17]	50 PAD/50 controls	Higher fibrinogen, vWF, PAI-1, tPA, P-selectin on both stimulated and non-stimulated platelets; lower PAI-1/tPA ratio
Lowe[18]	388 PAD/1581 controls	Higher blood viscosity, hematocrit, fibrinogen, leucocyte elastase, and uric acid; haematocrit and viscosity directly correlated with PAD severity
Makin[19]	234 PAD/50 controls	Higher soluble P-selectin, vWF, TF and fibrinogen; fibrinogen directly correlated with PAD severity
McDermott[20]	346 PAD/203 controls	D-dimer and hsCRP inversely correlated with limb function in both PAD and controls
Reininger[21]	92 PAD/70 controls	Higher platelet adhesion and aggregation, fibrinogen, fibrin monomer, d-dimer and TAT
Robless[22]	20 PAD/20 controls	Higher spontaneous and induced platelet aggregation
Zeiger[23]	50 PAD/50 controls	Higher P-selectin expression on platelets, platelet aggregates and platelet-derived microparticles

α1-AT, α 1-antitrypsin; α2-PI, α 2-plasmin inhibitor; CAD, cardiovascular disease; CVD, cerebrovascular disease; hsCRP, highly sensitive C reactive protein; PAI-1, plasminogen activator inhibitor 1; PF4, platelet factor 4; TAT, thrombin-antithrombin complex; TM, thrombomodulin; tPA, tissue plasminogen activator; vWF, von Willebrand Factor.

including trials in intermittent claudication (n = 26), peripheral bypass grafting (n = 12) and peripheral angioplasty (n = 4). The pooled odds reduction in major cardiovascular events for antiplatelet treatment in patients with PAD was 23% (p = 0.001), similar to the aggregate finding for all 195 trials included in the meta-analysis (odds reduction 22%, p<0.001). This robust evidence has often been cited to support aspirin treatment in patients with PAD, but careful examination of the individual trials shows that nearly 60% of the data relate to other antiplatelet agents. Thus the efficacy of aspirin in PAD must be extrapolated from other treatment trials in the ATC database. This does not necessarily mean that aspirin is ineffective in patients with PAD; indeed, the benefit of aspirin on cardiovascular events has been confirmed in a number of other high-risk settings as well as in primary prevention.[42]

More recently, Collins *et al*[43] reported a meta-analysis of aspirin and other antithrombotic agents after infrainguinal bypass graft. Of the 10 included trials, 7 compared antiplatelet agents with placebo and 3 compared oral anticoagulants with placebo. Six of the 7 antiplatelet trials studied aspirin or aspirin/dipyridamole. Antiplatelet treatment reduced the odds of graft occlusion by 57% (95% confidence interval (CI) 33 to 73), which was similar to the overall effect across all 10 trials (odds reduction 54%, 95% CI 34 to 68). Mortality was also significantly reduced (odds ratio (OR) 0.7, 95% CI 0.51 to 0.95). These benefits were accompanied by a non-significant

Table 2 Major randomised controlled trials of antithrombotic treatment in peripheral arterial disease

Study	Comparison	Patients	Efficacy for cardiovascular events
Aspirin			
MATCH[30]	ASA + clopidogrel *v* clopidogrel	7599 patients with stroke or TIA including 776 with PAD	Overall 6% reduction favouring dual treatment (p = 0.24); 20% reduction in PAD subgroup (p = NS)
McCollum[31]	ASA + dipyridamole *v* placebo	549 patients undergoing femoralpopliteal bypass	45% reduction favouring ASA + dipyridamole (p = 0.004)
Thienopyridines			
CAPRIE[32]	Clopidogrel *v* ASA	19 185 with atherosclerosis including 6452 with PAD	Overall 9% reduction favouring clopidogrel (p = 0.043); 24% reduction in PAD subgroup (*p* = 0.003)
CHARISMA[33]	Clopidogrel + ASA *v* ASA	15 603 with atherosclerosis including 2838 with PAD	Overall 7% reduction favouring clopidogrel (p = 0.22); 13% reduction in PAD subgroup (p = 0.29)
CREDO[34]	Clopidogrel + ASA *v* ASA	2116 patients including 272 with PAD or CVD	Overall 27% reduction favouring clopidogrel (p = 0.02); 48% reduction in PAD/CVD subgroup (p = 0.06)
EMATAP[35]	Ticlopidine *v* placebo	615 patients with claudication	74% reduction favouring ticlodipine (p = 0.002)
STIMS[36]	Ticlopidine *v* placebo	687 patients with claudication	Non-significant 11% reduction favouring ticlopidine (p = 0.24); 29% reduction in all-cause mortality (p = 0.015)
Thromboxane inhibitors			
ADEP[37]	Picotamide *v* placebo	2304 patients with claudication	Non-significant 19% reduction favouring picotamide (p = 0.056)
DAVID[38]	Picotamide *v* ASA	1209 patients with claudication and diabetes	Non-significant 18% reduction favouring picotamide (p = 0.30); 45% reduction in all-cause mortality (p = 0.047)
Oral anticoagulants			
Dutch BOA[39]	Coumarins* *v* ASA	2690 patients undergoing infrainguinal grafting	Non-significant 11% reduction favouring coumarins (p = 0.19)
WAVE[40]	Warfarin + ASA *v* ASA	2181 patients with symptomatic or asymptomatic PAD	Non-significant 8% reduction favouring warfarin + ASA (p = 0.49)

ADEP, atherosclerotic disease evolution by picotamide; ASA, acetylsalicylic acid; CAPRIE, Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance; CREDO, Clopidogrel for the Reduction of Events During Observation; CVD, cerebrovascular disease; DAVID, Drug evaluation in Atherosclerotic Vascular disease In Diabetics; Dutch BOA, Dutch Bypass Oral Anticoagulants or aspirin; EMATAP, Estudio Multicentrico Argentino de la Ticlopidine en las Arteriopatias Perifericas; MATCH, Management of Atherothrombosis with Clopidogrel in High-risk patients; NS, not significant; PAD, peripheral arterial disease; STIMS, Swedish Ticlopidine Multicentre Study; TIA, transient ischaemic attack; WAVE, Warfarin Antiplatelet Vascular Evaluation.
*Phenprocoumon or acenocoumarol.

Table 3 Characteristics of various antithrombotic treatments

Treatment	Advantages	Disadvantages
Aspirin	Large evidence base for prevention of vascular events Excellent cost effectiveness	Gastrointestinal intolerance, bleeding and allergy Efficacy in several comparative trials was inferior to other agents
Clopidogrel	Efficacy in patients with coexisting CAD Marginal benefit over aspirin possibly amplified in PAD	Less cost effective than aspirin Evidence in PAD is limited to subgroup analyses
Picotamide	Enhanced efficacy in PAD with concomitant diabetes Favourable effects on claudication symptoms	Inconvenient dosing schedule (twice daily) Unavailable in many settings
Ticlopidine	Established efficacy in patients with PAD Favourable effects on claudication symptoms	Haematological toxicity significantly greater than clopidogrel Inconvenient dosing schedule (twice daily)
Coumarins	Reduced graft occlusion after revascularisation Coexisting indications (eg, atrial fibrillation, deep vein thrombosis, mechanical heart valves)	Efficacy in PAD is not superior to antiplatelet treatment Higher rates of serious haemorrhage than antiplatelet treatment Complexity of treatment and requirement for monitoring

CAD, coronary artery disease; PAD, peripheral arterial disease.

trend towards increased bleeding (OR 1.82, 95% CI 0.43 to 7.73). Given the predominance of aspirin trials in this analysis, these data support aspirin-based prophylaxis in patients with PAD.

Additional advantages of aspirin are its affordability (about US$0.04/dose), wide availability, ease of dosing and lack of necessity for therapeutic monitoring. The main disadvantages are gastrointestinal intolerance in a substantial number of patients and, more importantly, the high residual risk of cardiovascular events despite long-term treatment. The latter has spurred the investigation of other antithrombotic approaches for patients with PAD (and indeed other forms of atherosclerosis). The most common non-aspirin antiplatelets studied in this setting have been ticlopidine, clopidogrel and picotamide. An additional rationale for investigating these drugs is that they inhibit disparate mechanisms of platelet activation and may thus provide complementary antiplatelet activity.

Thienopyridines

Ticlopidine and clopidogrel are members of the thienopyridine class of antiplatelet agents, which act by blocking the adenosine diphosphate-mediated pathway of platelet activation. A meta-analysis of ticlopidine treatment in patients with intermittent claudication suggested a significant benefit on mortality (OR 0.68, 95% CI 0.49 to 0.95) and need for revascularisation (OR 0.62, 95% CI 0.41 to 0.93).[44] Another meta-analysis in patients undergoing lower limb procedures for PAD showed a substantial reduction in postoperative reocclusion favouring active treatment (OR 0.53, 95% CI 0.33 to 0.85) and a near-significant reduction in amputation (OR 0.29, 95% CI 0.08 to 1.01).[45] On the other hand, no adequately powered randomised trial has compared ticlopidine with other effective antiplatelets in patients with PAD, and ticlopidine has largely been supplanted by clopidogrel due to the risk of life-threatening neutropenia with ticlopidine.

Some evidence suggests that the presence of PAD may identify a subset of patients more likely to benefit from clopidogrel treatment. For example, in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events trial, clopidogrel reduced the risk of cardiovascular events by 9% in comparison with aspirin (95% CI 0.3 to 17; $p = 0.043$).[32] However, among the 6452 patients enrolled on the basis of PAD the risk reduction was nearly three times greater (24%; 95% CI 9 to 36; $p = 0.003$) and a formal test of interaction for this subgroup effect was significant ($p = 0.042$).

Similar findings of incremental benefit were noted in the Clopidogrel for the Reduction of Events During Observation study, in which clopidogrel plus aspirin was compared with aspirin alone in patients with coronary artery disease scheduled for percutaneous intervention.[34] Patients with concomitant extracoronary vascular disease (defined as peripheral or cerebrovascular atherosclerosis) had a > 2-fold greater risk reduction for the primary end point compared with patients who did not have extracoronary vascular disease (OR 48%, 95% CI −4 to 74, *v* OR 18%, 95% CI −11 to 40, respectively). In addition, the incidence of major cardiovascular events (death, myocardial infraction, stroke or urgent revascularisation) was significantly reduced, from 19.6% to 9.2%, in patients with extracoronary vascular disease ($p = 0.02$, absolute risk reduction 10.4%). A similar trend for increased benefit by presence of PAD was found in the Management of Atherothrombosis with Clopidogrel in High-risk Patients (MATCH) study.[30] However, in the most recent study of long-term clopidogrel for the prevention of atherothrombosis (CHARISMA: Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance), there was no benefit for clopidogrel on cardiovascular events either overall (RR 0.93, 95% CI 0.83 to 1.05) or among the 3531 patients enrolled with PAD (RR 0.87, 95% CI 0.67 to 1.13).[33]

Thromboxane antagonists

Picotamide is an agent with inhibitory effects on thromboxane A2 synthase and thromboxane A2/prostaglandin endoperoxide H2 receptors on platelets. Three small, early randomised trials suggested that picotamide lowers the risk of cardiovascular events in patients with acute myocardial infarction, previous ischaemic stroke or diabetes.[46–48] Two larger randomised studies studied the efficacy of picotamide in patients with PAD, against either placebo[37] or aspirin.[38] In the placebo-controlled study, picotamide did not reduce the risk of cardiovascular events in the intention-to-treat analysis (OR 0.80, 95% CI 0.63 to 1.01; $p = 0.057$), although a suggestion of benefit was found in the on-treatment analysis (OR 0.76, 95% CI 0.59 to 0.97; $p = 0.029$).[37] A more substantial reduction was found in a small subgroup of patients with both PAD and diabetes (OR 0.52, 95% CI 0.24 to 0.74; $p = 0.022$), but this analysis was conducted and reported retrospectively.[49]

Building on the latter finding, a subsequent randomised study compared picotamide with aspirin specifically in patients with PAD and diabetes.[38] The primary end point, all-cause mortality, was reduced by 45% in patients allocated to picotamide (95% CI 2 to 69; $p = 0.047$). However, the principal secondary end point of total morbidity and mortality (comprising myocardial infarction, stroke, major amputation and death) was not reduced ($p = 0.3$). Of additional concern, morbidity and mortality data were unavailable for 18% and 5% of patients, respectively. Further hampering the applicability of these findings, picotamide is currently unavailable in many countries.

Oral anticoagulants

Updating previous evidence, Anand *et al* recently reported a meta-analysis of nine randomised trials of oral anticoagulants (OAC) involving 4889 patients.[50] Compared with control (no treatment), OAC reduced the risk of graft occlusion by 37%

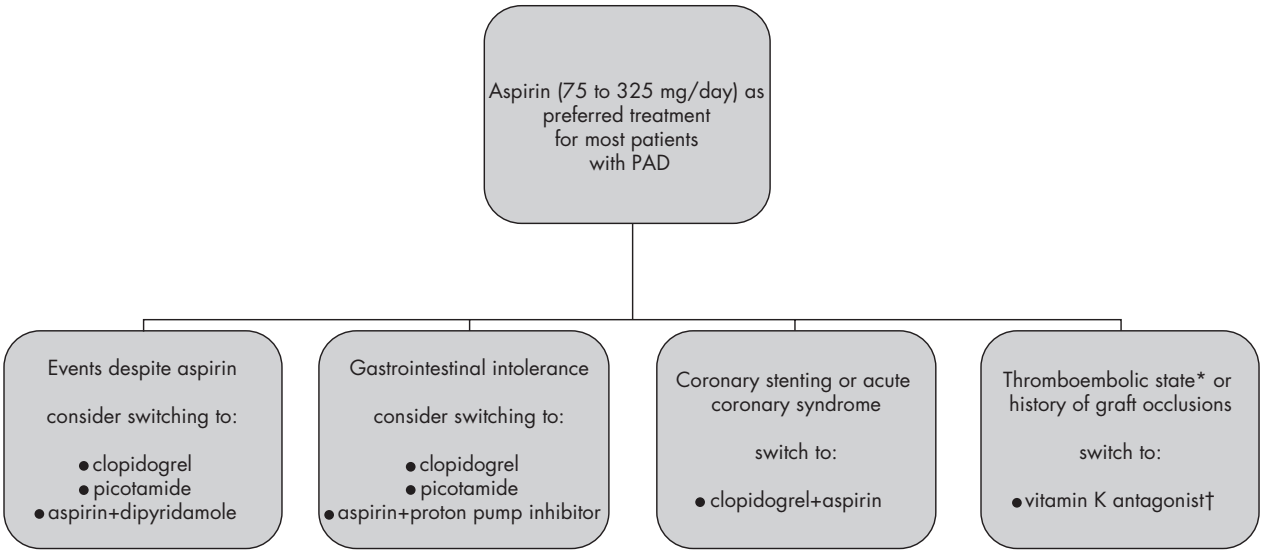

Figure 1 Selection of antithrombotic treatment in patients with peripheral arterial disease. *Atrial fibrillation, mechanical heart valve, underlying thrombophilia, or venous thromboembolism. †Oral coumarin plus aspirin in patients with mechanical heart valves. PAD, peripheral arterial disease.

(95% CI 11 to 56) with a trend towards decreased mortality (OR 0.73, 95% CI 0.5 to 1.07). The risk of major haemorrhage was substantially higher among OAC-allocated patients (OR 3.64, 95% CI 2.03 to 6.56). When compared with aspirin, OAC was not more effective in preventing graft occlusion or death (OR 0.91, 95% CI 0.77 to 1.06; and OR 1.04, 95% CI 0.85 to 1.29, respectively); moreover, the risk of major haemorrhage was nearly doubled (1.96, 95% CI 1.43 to 2.69). Finally, the combination of OAC plus aspirin was not more effective than aspirin alone, with higher rates of mortality and major haemorrhage (OR 1.57, 95% CI 1.16 to 2.12; and OR 2.13, 95% CI 1.27 to 3.57, respectively) and no reduction in graft loss (OR 0.84, 95% CI 0.62 to 1.12).

Since this meta-analysis, a large randomised trial (n = 2161) comparing the combination of moderate intensity warfarin treatment (median INR 2.2) and aspirin with aspirin alone has been completed.[40] There was no difference between the two arms in the primary end point of cardiovascular death, myocardial infarction or stroke (RR 0.92, 95% CI 0.73 to 1.16). On the other hand, life-threatening bleeding (defined as bleeding that was fatal, intracranial or required surgical intervention or the transfusion of at least 4 units of blood products) was increased by more than threefold (RR 3.41; 95% CI 1.84 to 6.35) and haemorrhagic stroke by more than 15-fold (RR 15.2, 95% CI 2 to 115.6). Together these data suggest that oral anticoagulants should not be preferred to antiplatelet agents for the routine treatment of PAD; additional disadvantages include the inconvenience of treatment, poor adherence, potential for drug and food interactions, and the requirement for laboratory monitoring and dose titration.

RECOMMENDATIONS AND SUMMARY

In terms of affordability, safety and efficacy, aspirin remains the first-line agent for most patients with PAD (table 3). However, there are a number of scenarios in which other agents might be considered (fig 1). For example, patients who experience vascular events while on aspirin should probably be switched to clopidogrel or picotamide. Patients with a history of stroke might particularly benefit from dual treatment with aspirin and dipyridamole, as suggested by the recent European/Australasian Stroke Prevention in Reversible Ischaemia trial, the favourable results of which are in line with previous randomised trials in PAD.[31 51] Gastrointestinal intolerance to non-steroidal anti-inflammatory agents may be another reason to select clopidogrel or picotamide, although a reasonable and proved option would be to combine aspirin with a proton pump inhibitor.[52] Patients with PAD who undergo coronary stenting or who have acute coronary syndrome should be prescribed dual treatment with clopidogrel and aspirin, on the basis of strong efficacy in randomised trials.[53] Finally, moderate intensity warfarin treatment (target international normalised ratio 2.5) would be acceptable in the presence of coexisting indications such as atrial fibrillation or recent venous thrombosis, although it might also be considered for patients with a history of peripheral graft occlusion.[29]

Although chronic antithrombotic prophylaxis should be prescribed to nearly all patients with PAD, many studies suggest widespread underutilisation of this efficacious strategy, with treatment gaps ranging from 25% to >50%.[54–57] In addition to increased use, other approaches are needed to combat the risk of cardiovascular events posed by this disease. Randomised trials have supported the efficacy of statins and antihypertensive agents for preventing vascular events in individuals affected by PAD.[58 59] These approaches should be coupled with intensive lifestyle modification, including structured exercise, prudent diet and smoking cessation. Recent cohort studies have suggested remarkable efficacy from combining these strategies in patients with PAD, suggesting that far from being fatalistic, doctors encountering PAD should be optimistic that they possess effective tools for comprehensively managing this condition.[60 61]

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IMAGES IN CARDIOLOGY

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Angina during upper limb exercise: pathognomonic clinical feature of coronary–subclavian steal syndrome?

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A 62-year-old patient, with a history of myocardial revascularisation consisting of a left internal mammary artery (LIMA) to the left anterior descending coronary artery (LAD) for significant coronary artery disease 16 years ago, was admitted with intermittent chest pain occurring only during physical activity of the left arm. The stress ECG up to 175 W was negative for ischaemic signs. His blood pressure was 120/70 mm Hg in the right arm and 60/40 mm Hg in the left arm. Non-invasive evaluation by magnetic resonance tomography (Angio-Surf) demonstrated a complete occlusion (panel A) of the left subclavian artery (LSA), which was confirmed by aortography (panel B). Selective injection of a contrast agent into the left main coronary artery revealed coronary–subclavian steal syndrome (CSSS) demonstrated by reverse flow from the LAD through the LIMA into the LSA (panel C). Complete recanalisation of the occluded LSA with subsequent antegrade flow into the LIMA (panel D) was achieved by percutaneous angioplasty and stent implantation (Biotronik, 8×25 mm, 14 atm insufflation pressure) without any complications of cerebral or myocardial ischaemia. His symptoms disappeared and his blood pressure in the left arm was thereafter equal to that in the right arm.

Chest pain only during physical exercise of the left arm in patients with a history of LIMA-to-LAD bypass graft may be pathognomonic for CSSS, representing the clinical correlation of retrograde flow into the LIMA, with resultant coronary ischaemia. Percutaneous transluminal revascularisation by mean of stent implantation is the treatment of choice and can be successfully performed in such cases.